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A Composite Approach That Includes Dropout Rates When Analyzing Efficacy Data in Clinical Trials of Antipsychotic Medications

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Background: **Often, outcomes in clinical trials of antipsychotic medications are examined using last observation carried forward (LOCF). One limitation of LOCF and other common approaches is that they overlook the meaning underpinning trial completion and noncompletion. Noncompletion often relates to lack of drug tolerability. Because long-term treatment is often indicated, noncompletion is an important outcome. An alternative approach is to test the composite hypothesis of the difference between (a) completion rates and (b) efficacy of complete cases. Studies to date have not applied this relatively new method.** ***Objective:*** **To illustrate the composite approach, we applied it to a systematic review of studies and compared the results with the reported LOCF analysis.** ***Methods:*** **A systematic search of the Schizophrenia Module of the Cochrane Library and Medline was conducted that identified 127 relevant randomized clinical trials of antipsychotic medications conducted since 1995. Extracted from study reports were the *P* values of a difference in dropout and the *P* value of a difference in improvement among complete cases. These *P* values were combined using standard approaches.** ***Results:*** **We identified 11 trials with 5339 participants that provided the necessary information to adequately apply the composite approach. In 2 trials, (18.2%) in which the LOCF results were not significant, the composite results were significant.** ***Conclusions:*** **The composite approach was more sensitive to change than LOCF and conceptually answers a more relevant question. It is likely that applying the composite approach would change how results of many trials are interpreted.**

Key words: clinical trials/missing data/last observation carried forward/composite approach

Introduction

Dropout is a major cause of missing data in clinical trials generally and trials of antipsychotic medications in particular. It creates uncertainty in interpreting study results. It is not uncommon for dropout rates in these studies to exceed 50%.[1,2] For example, in the recent landmark Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study [3] overall, 74% of trial participants discontinued the study medication before the planned 18 months (1061 of the 1432 patients who received at least one dose). Dropout is also an important outcome because it may reflect a lack of drug tolerability or adverse effects or lack of compliance. Due to the recognition of the importance of dropout, it was included as an a priori outcome in CATIE.

Dropout leads to missing data that varies as to the extent to which it affects modeling and analysis. The literature distinguishes between 3 mechanisms of missing data.[4] First, *missing completely at random* (MCAR) that refers to a situation where missingness does not depend on either the observed or unobserved data. A possible example is data lost because some patient records were destroyed in a flood. MCAR can readily be handled in the analysis using standard approaches. Nevertheless MCAR leads to loss of power due to diminished sample size. Second, *missing at random* (MAR) that occurs if the missing data depends on variables that are observed during the trial and not on unobserved data. An example of MAR could be increased dropout in the placebo arm of a study or high dropout rates in a particular study center. In such cases, dropout is explained by the observed data and can be accounted for in the data analysis. Third, *missing not at random* (MNAR) that occurs if the missingness depends on unobserved data. An example could be a patient who was improving and then was lost to follow-up because he had relapsed after the last observed visit and was admitted to a different hospital. In this case, the observed data could not predict the missing data. The unobserved data contained information not foreseen by the observed data.[5] MNAR cannot be corrected without explicitly specifying a model for the missing data mechanism, which by definition cannot be tested.

MCAR and MAR are termed *ignorable nonresponse* because the first requires no special attention when

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analyzing the data and the second can be controlled for in the analysis. MNAR is termed *nonignorable nonresponse* because it cannot be ignored. MAR and MNAR are also sometimes referred to as "informative" because the data that is missing is informative as it relates to study variables.

Missing data in clinical trials of antipsychotic medication because of dropout are problematic because they are rarely MCAR and it is generally difficult to determine if they are MAR or MNAR. A standard approach used in clinical trials is the last observation carried forward (LOCF). LOCF uses the last completed observation while on treatment to estimate a hypothetical last visit value. This is problematic because it assumes that the data are MCAR and that symptoms would have remained stable until the end of the trial. Some recent trials [3,6,7] have applied a mixed-effects model[5] that is thought to provide more accurate estimates of treatment than LOCF.[5] These estimates are based on data available at each given time point. Mixed-effect models and imputation methods work if data is MCAR or MAR; however, if the data is MNAR then inferences based on these methods will not be valid.

The above highlights that when using standard approaches, the mechanism of missing data is of critical importance. However, an alternative and newer approach has been proposed to address the dropout problem[8] that can be applied regardless of the missing data mechanism. This approach, which is illustrated in table 1 and explained in detail later, tests a combination of 2 hypotheses stating that patients will complete the trial and that patients who complete the trial will improve. Accordingly, this is termed the composite approach. Specifically, this approach[8] combines the *P* value of the difference in completion rates between drug treatments and the *P* value obtained in comparing the difference in treatment outcomes of complete cases. The approach gives a single *P* value that reflects both outcomes. If the result is statistically significant, it means that the groups differ on the combined hypothesis. Thus, when the null hypothesis is rejected, the conclusion is that the chance of completing the trial and/or the treatment effect given completing the trial is superior.

The novelty of the composite approach is that it allows testing for differences between treatment groups without imputing data or making assumptions about the missing data mechanism. The composite approach provides a statistically more powerful test than testing both measures separately. Also, conceptually it is more meaningful to examine these 2 outcomes together because symptom improvement without study completion is generally not a favorable outcome. As a way of demonstrating the composite approach, we compared the results obtained using the composite approach with those reported in the literature. Common to most trials is LOCF and was thus our basis for comparison.

Methods and Materials

Study Selection

To obtain studies, we conducted a systematic search of the Schizophrenia Module of the Cochrane Library and Medline seeking randomized clinical trials of second-generation (atypical) antipsychotic medications reported from 1995 to July 2006. This identified 127 such clinical trials. Extracted from study reports were the number of patients in each study arm, the number of these patients who completed the trial, the *P* value of the analysis of patients who completed the study (ie, completers analysis), and the *P* value of the LOCF analysis. All studies with at least 30 patients per arm were included. This resulted in a total of 5339 study participants.

Data Analysis

To index the difference in completion rates for each pair of comparisons in the studies, we computed chi square as a test of difference in proportions. We then combined that *P* value with the reported *P* value of the analysis of complete cases. Based on a series of theorems and proofs, Shih and Quan[9] have shown the independence of these *P* values. We therefore used accepted approaches for combining *P* values of independent tests. Our primary approach was adding logs.[8,10] To examine the sensitivity of the results to this method of combining *P* values, we also applied the following additional approaches: (1) adding *P* values,[11] (2) adding *t* values,[12] (3) adding *z* values,[13] (4) adding weighted *Z* values,[13] and (5) minimum *P* values.[14] The methods are presented and illustrated in table 1 and detailed elsewhere.[15,16]

Table 1 presents the method and formulae and works through an example of applying the methods to one of the studies reviewed later in this article (second trial presented in table 2). In the example in table 1, for Drug A, 49 of 202 patients dropped out and for Drug B, 79 of 264 patients dropped out. A chi-square test showed the difference in completion rates to be $P = .087$. A complete cases analysis found a difference on the efficacy measure of $P = .105$ favoring Drug A. Thus, Drug A had a nonsignificant ($P < .05$) advantage in both completion rates and efficacy. In the example, the standard LOCF analysis found the same direction of difference with a high *P* value ($P = .86$) implying no difference in efficacy between the drugs. The example shows that all methods except for the minimum *P* approach would support, unlike the LOCF analysis, the superiority of Drug A over Drug B. Thus, excluding the minimum *P* approach, the methods are very similar indicating that LOCF is not sensitive to dropout. The adding *t* and weighted *Z* values approaches differ because they weigh the tests by the number of subjects in the analysis. The minimum *P*-value approach while similar to some methods of multiple hypothesis testing is applied here to combine *P* values to test a global null hypothesis.

Table 1. Methods to Combine *P* Values

Method	Formula (*N* = Number of Groups)	Example: Drug A (*n* = 202), 49 Dropped Out and 153 Completed; Drug B (*n* = 264), 79 Dropped Out and 185 Completed; Comparison of Dropout: *P* = .087 (1-tailed), *df* = 464; Completers Analysis: a > b, *P* = .105 (1-tailed), *df* = 338; LOCF: *P* = .86, *df* = 464
Adding logs[10]	$\chi^2(df = 2N) = \sum -2 \ln P$	$\chi^2(df = 4) = (4.88 + 4.58)$, $P = .052$
Shih and Quan[8] variation on adding logs	$P = P(d) \times P(e) \times (1 - \ln(P(d) \times P(e))$, where $P(d)$ is the P value of difference in dropout and $P(e)$ is the P value of difference in completers analysis of efficacy.	$.087 \times .105 \times (1 - \ln(.087 \times .1)) = .052$
Adding probabilities[11]	$\frac{(\sum P_i)^N}{N!}$	$\frac{(.087 + .101)^2}{2} = .018$
Adding *t*s[12]	$Z = \frac{\sum t_i}{\sqrt{\sum [df/(df-2)]}}$	$t(.087, df = 464) = 1.36$; $t(.101, df = 338) = 1.23$; $Z = \frac{1.36 + 1.23}{\sqrt{464/(464-2) + 338/(338-2)}}$; $Z = 2.70$, $P = .013$
Adding *Z*s (Stoufer method)[13]	$Z = \frac{\sum Z_i}{\sqrt{N}}$	$\frac{1.36 + 1.23}{\sqrt{2}} = \frac{2.59}{1.41} = 1.83$; $Z = 1.83$, $P = .032$
Adding weighted *Z*s[13]	$Z = \frac{T}{W} = \frac{df_1 Z_1 + df_2 Z_2}{\sqrt{df_1^2 + df_2^2}}$, W = weight by sample size for test	$\frac{(464 \times 1.36) + (338 \times 1.23)}{\sqrt{(464^2 + 338^2)}} = \frac{1047}{574} = 1.82$; $P = .032$
Minimum *P* value[14]	$1 - (1 - \text{alpha})^{1/k}$, k = number of *P* values being combined	$1 - (1 - .05)^{.5} = .025$. Null hypothesis is not rejected because lowest *P*, .087, is greater than .025.

Note: LOCF, last observation carried forward.

Results

Table 2 presents 11 of the 12 studies that met the study criteria to apply the composite approach. In 2 studies,[17,18] the LOCF analysis (presented in the far right column) did not show a significant difference between the trial arms, but all or most of the remaining methods demonstrated a significant difference. Specifically, in one study[18] the LOCF difference was $P = .18$ whereas all the P values were $P < .00001$ and the minimum P approach supported a difference because the smallest P (.0001), as well as the largest in this case (.0025) were smaller than .025. In another trial,[17] the LOCF test was $P = .86$. Yet the P values for the combined tests were between .052 and .013. The minimum P approach, however, did not support a significant difference between trial conditions. In 6 trials,[19–24] significant differences were found in the LOCF analysis and on all or almost all the combination approaches. In another trial,[25] LOCF and 4 combined approaches were significant or nearly significant and 2 were not ($P = .13$, $P = .15$). In 2 trials,[26,27] significant differences were neither found on LOCF nor on any of the combination approaches. One final study, not shown in table 2, gave results that are difficult to interpret because one drug had higher dropout but more improvement; thus, combining tests in this case is not appropriate. Not shown, the second method[8] for adding logs gave identical results. Collectively, these results indicate that the composite approach led to different conclusions as compared with the planned LOCF analysis in some of the studies.

Discussion

We have applied the composite approach that is an overall measure of evidence to account for both efficacy and dropout. We have illustrated the application of the composite approach and have compared it with results obtained using the traditional LOCF in clinical trials of antipsychotic medication. The results demonstrated that were the composite approach to have been adopted in 2 of the 12 studies analyzed the conclusions of the studies would have been different. In one study[28] where the directions of the tests were not consistent (ie, dropout and efficacy were higher in the same study), the data would need further consideration similar to a situation where 2 efficacy measures gave opposite results.

Although a systematic search of the literature has been conducted, a vast majority of the studies did not present sufficient information (ie, completers analysis and number

Table 2. Applying Composite Approach to Existing Clinical Trials of Antipsychotic Medication

Authors, Planned Comparison (Measure)	Dropout			Completers Analysis	Combining *P* Values						
	Drug A	Drug B	Chi-Square *P*(d) 1-tailed (difference favoring)	*P*(e) 1-tailed (difference favoring)	Adding logs	Adding *P*s	Adding *T*s	Adding *Z*s	Adding Weighted *Z*s	Min *P*	LOCF 2-tail
LOCF $P > .05$; combining $P < .05$											
Breier and Hamilton,[18] olanzapine vs haloperidol (PANSS)	35% (124/352)	52% (90/174)	.0001 (a > b)	.0025 (a > b)	0.000004	.00000	0.00000	0.00000	0.00000	a > b	0.18 (a > b)
Keks et al,[17] long-acting injectable risperidone vs olanzapine (PANSS)	24% (49/202)	30% (79/264)	.087 (a > b)	.105 (a > b)	0.052	.01843	0.01261	0.03232	0.05045	b <> a	0.86 (a > b)
LOCF $P < .05$; combining $P < .05$											
Lauriello et al,[19] long-acting injectable risperidone vs placebo (PANSS)	60% (96/161)	83% (44/53)	.0009 (a > b)	.007 (a > b)	0.00009	.00003	0.00000	0.00004	0.00010	a > b	0.001 (a > b)
Kane et al,[20] long-acting injectable risperidone 25 mg vs placebo (PANSS)	53% (52/99)	69% (68/98)	.008 (a > b)	.0005 (a > b)	0.00005	.00004	0.00000	0.00003	0.00030	a > b	0.002 (a > b)
50 mg vs placebo (PANSS)	50% (51/103)	69% (68/98)	.007 (a > b)	.01 (a > b)	0.0007	.00014	0.00000	0.00036	0.00082	a > b	0.001 (a > a)
75 mg vs placebo (PANSS)	52% (52/100)	69% (68/98)	.009 (a > b)	.026 (a > b)	0.002	.00061	0.00003	0.00116	0.00182	a > b	0.001 (a > b)
Danion et al,[21] amisulpride 50 mg/d vs placebo (SANS)	17% (14/84)	40% (33/83)	.0005 (a > b)	.028 (a > b)	0.0002	.00041	0.00000	0.00012	0.00008	a > b	0.0007 (a > b)
100 mg/d vs placebo (SANS)	20% (15/75)	40% (33/83)	.0035 (a > b)	.01 (a > b)	0.0004	.00009	0.00000	0.00019	0.00020	a > b	0.0006 (a > b)
Amisulpride 50 mg/d vs amisulpride 100 mg/d (SANS)	17% (14/84)	20% (15/75)	.293 (a > b)	.285 (b > a)	0.29	.16704	0.21410	0.21570	0.21738	a <> b	0.84 (b > a)
Beasley et al[22] olanzapine 15 mg/d (high dose) vs haloperidol (SANS)	51% (35/69)	57% (39/69)	.247 (a > b)	.025 (a > b)	0.038	.03699	0.01034	0.03077	0.07559	a > b	0.015 (a > b)
Wetzel et al,[23] amisulpride 1000 mg/d vs flupentixol 25 mg/d (BPRS)	27% (19/70)	40% (25/62)	.0545 (a > b)	.167 (a > b)	0.05	.02311	0.01306	0.03325	0.02977	a <> b	0.05 (a > b)
Tollefson et al,[31] olanzapine vs haloperidol (PANSS)	34% (448/1336)	53% (351/660)	.0001 (a > b)	.0015 (a > b)	0.000002	.00000	0.00000	0.00000	0.00000	a > b	0.05 (a > b)
LOCF $P < .05$; combining $P < .05$ and $P > .05$											
Hale,[25] sertindole vs haloperidol (PANSS)	40% (48/120)	39.8% (49/123)	.4897 b <> a	.025 (a > b)	0.066	.13246	0.05314	0.08014	0.15210	a > b	0.05 (a > b)
LOCF $P > .05$; combining $P > .05$											
Tollefson et al,[26] olanzapine vs clozapine (PANSS)	40% (36/90)	41% (37/90)	.4397 (a > b)	.181 (a > b)	0.282	.19326	0.22577	0.22687	0.27696	a <> b	0.34 (a > b)
Conley et al,[27] olanzapine vs chlorpromazine (BPRS)	29% (12/42)	31% (13/42)	.406 (a > b)	.105 (a > b)	0.177	.13056	0.12710	0.14581	0.18120	a <> b	0.25 (a > b)

Note: LOCF, last observation carried forward; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; BPRS, Brief Psychiatric Rating Scale.

of dropouts) to utilize the composite approach. Therefore, it is not possible to conjecture the extent to which a composite approach would have altered major conclusions in the field. The composite approach highlights the importance of reporting both dropout rates and completers analysis, which, as our review showed, are not routinely reported. In addition to the combined test, each is important as well. Some of the differences reported using the composite approach were large and others were small. We envision the composite approach being included a priori as part of the planned statistical analysis that would specify how the results are to be interpreted.

A limitation of our application of the composite approach is that because we did not have the data sets for the reviewed studies, we were unable to test for possible baseline differences between the completers in the treatment groups within each trial and to control for them as suggested by Shih and Quan.[8] This may have introduced a bias in some of the P values. The approach, as we have applied it, assumes that improvement and dropout are of equal importance. Differential weighting, however, can be used to give the desired relative importance to either outcome. This can be done using the adding weighted Zs[13] method and substituting sample size with the desired weighting. It can also be done using other methods such as the joint testing approach proposed by McMahon and Harrell.[29]

The composite approach can also be used to combine other key measures with dropout. For example, other efficacy measures, measures of EPS, and quality of life may be combined with dropout to form a single statistical test. The composite approach is applicable to many other areas also plagued by high dropout rates, where dropout is informative (eg, longitudinal studies of Alzheimer disease and IQ among the elderly; clinical trials of cancer; acquired immunodeficiency syndrome, etc.). It is noted that noncompletion may not exclusively reflect failure of treatment but also quality of care. The quality of care, however, is unlikely to differ between randomized treatments in the same study. We note that while noncompletion is not always due to lack of efficacy, we view dropout for almost any reason to be a nondesirable outcome and thus did not focus on reasons for dropout.

The composite approach can also be extended to dichotomous outcomes, such as clinical improvement that is sometimes defined as 20% improvement on symptom measure. The dichotomous outcome of completion is combined with clinical improvement. Using this approach on the Keks et al[17] study, eg, we found[30] that when completion and improvement were combined, 66.1% (133/201) of the patients getting long-acting injectable risperidone both completed the trial and improved as compared with 53.7% (142/264) of olanzapine-treated patients ($P < .005$). Other studies that we reviewed did not report this data on complete cases, so the approach could not be applied for those studies.

In summary, unlike standard approaches the composite approach can be applied without having to be concerned about missing data. The composite approach examines not only change in symptoms but also dropout rates. It tests the joint hypothesis of a difference in rates of completion and efficacy among complete cases. Therefore, it provides meaning beyond LOCF and other methods that ignore the meaning of not completing a trial and do not adequately account for the missing data mechanism. Like many other drug treatments, for antipsychotic medications to be effective they need to be taken continuously, hence dropout is a poor outcome. The composite approach provides sensitive information and produces significant and accurate results making it appropriate to include in planned analysis.

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